MICROALBUMINURIA – AN EARLY MARKER FOR CHRONIC KIDNEY DISEASE AMONG JUVENILE DIABETICS - A STUDY

Dissertation Submitted for

MD Degree (Branch VII) PEDIATRICS

April 2012

The Tamilnadu Dr.M.G.R.Medical University

Chennai – 600 032.

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"MICROALBUMINURIA – AN EARLY MARKER FOR CHRONIC KIDNEY DISEASE AMONG JUVENILE DIABETICS - A STUDY"** submitted by **Dr.K.RAMYA** to the faculty of Pediatrics, The Tamil Nadu Dr.M.G.R Medical University, Chennai in partial fulfillment of the requirement for the award of M.D. Degree Branch VII (Pediatrics) is a bonafide research work carried out by her under our direct supervision and guidance.

r.CHITRA AYYAPPAN
M.D., DCH.,FRCP.,FRCPCH.,
Professor of Pediatrics
Institute of Child Health
& Research Centre,
Madurai Medical College,
Madurai.

Dr.P.AMUTHA RAJESWARI
M.D.,D.CH.,
Director & Professor of Pediatrics
Institute of Child Health
& Research Centre,
Madurai Medical College,
Madurai.

DECLARATION

I**, Dr.K.RAMYA** solemnly declare that the dissertation titled **"MICROALBUMINURIA –AN EARLY MARKER FOR CHRONIC KIDNEY DISEASE AMONG JUVENILE DIABETICS - A STUDY"** has been prepared by me. This is submitted to **The TamilNadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the regulations for the award of M.D. Degree Branch VII (Paediatrics).

Place: Madurai **Dr.K.RAMYA**

Date:

ACKNOWLEDGEMENT

My sincere thanks to the Dean, Government Rajaji Hospital and Madurai Medical College, Madurai for permitting me to do this study. I express my sincere thanks and gratitude to ***Prof.Dr.P.Amutha Rajeswari,*** Director & Professor of Pediatrics for her able guidance, encouragement, valuable suggestions and support for this study.

I am greatly indebted to my chief ***Prof.Dr.ChitraAyyappan***, Professor of Pediatrics for her excellent guidance, able supervision, critical review, constant encouragement and full support rendered in every aspect of this study.

I would like to sincerely thank ***Prof.Dr.G.Mathevan, Prof.Dr.R.A.Sankara Subramanian, Prof. Dr.M.Nagenderan, Prof. Dr.S.Venkateswaran*** and ***Prof. Dr.S.Sambath*** for their valuable advice and encouragement.

I extend my heartfelt thanks to ***Prof. Dr.Arthur Asirvatham,*** Professor and Head of the Department for permitting me to take up this study in the department of Diabetology.

I wish to express my sincere thanks to my Assistant Professors of Pediatrics ***Dr.M.Kulandaivel, Dr.Nandini Kuppusamy, Dr.M.Saravanan and Dr.P.Guna*** for their guidance, supervision, valuable suggestions and support throughout this study.

I thank the ethical committee for granting me the permission to conduct the study.

I submit my heartfelt thanks to the children and their parents for extending full co-operation to complete my study successfully.

I thank the ***Media Nett,*** K.K.Nagar for processing this Dissertation work.

CONTENTS

INTRODUCTION

Type 1 Diabetes mellitus is a chronic metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature due to deficient insulin secretion. It is the most common endocrine – metabolic disorder of childhood and adolescence , with important consequences of physical and emotional development.

Morbidity and mortality stem from acute metabolic derangements and from long term complications that affect small and large vessels resulting in retinopathy,nephropathy,neuropathy,ischemic heart disease and arterial obstruction.

Diabetic nephropathy accounts for significant reduction in life expectancy of diabetic patients. It is the leading cause of end stage renal disease and accounts for 50 % of deaths.The progression of diabetic nephropathy from the appearance of clinical proteinuria to end stage renal failure is usually irreversible without any intervention. Approximately 80% type 1 diabetic patients with persistent microalbuminuria develop overt nephropathy after 10 to 15 yrs. Eventually 50% of these develop end stage renal disease within 10 yrs and 75% by 20 yrs.

The earliest detectable change in the course of diabetic nephropathy is the thickening in the glomerulus. At this stage ,the kidney may leak more serum albumin than normal in the urine and this can be detected by sensitive medical tests for albumin. This stage is called microalbuminuria.Hence it is considered as an early marker of diabetic nephropathy (Chronic kidney disease).In other words, the term microalbuminuria has been used to describe the amount of albumin in the urine which is less than that can be detected by ordinary clinical tests such as albustix but is otherwise still associated with future disease.According to the Gento Monticatini convention , microalbuminuria is said to be present when urine albumin excretion rate is 30 to 300 mg/24 hr or more than 20 mg/l in a spot sample. This is the incipient stage of diabetic nephropathy and it is totally reversible. Once overt proteinuria develops, the disease process becomes irreversible.

Early medical treatment with ACE inhibitors and lifestyle modification have been shown to halt the progress from micro to macroalbuminuria and eventually End Stage Renal Disease (ESRD). Therefore detection of microalbuminuria as early as possible in the course of disease is very important.

REVIEW OF LITERATURE

Diabetic nephropathy is also known as Kimmelstiel Wilson syndrome and it was discovered in 1936 by Clifford Wilson and Paul Kimmelstiel. Diabetic nephropathy occurs as a result of an interaction between hemodynamic and metabolic factors[(1)].

EPIDEMIOLOGY

Diabetic nephropathy affects approximately one third of people with type 1 or type 2 diabetes mellitus. Risk factors affecting progression of kidney disease include baseline albumin excretion, age, glycemic control, blood pressure, serum cholesterol and use of renin-angiotensin system blockers. As the total number of people with diabetes is projected to increase substantially by 2050, the prevalence of diabetic nephropathy will rise dramatically, with concomitant increase in associated cardiovascular mortality and end stage renal disease. This will produce significant social and economic ramifications, particularly in the developing world.

Natural History of Diabetic Nephropathy

The earliest clinical evidence of nephropathy is the presence of microalbuminuria . It occurs in 30% of type 1 diabetics 5 to 15 years after diagnosis but may be present at diagnosis in type 2 diabetics as the time of onset of type 2 diabetes is often unknown. Microalbuminuria progresses to

proteinuria over the next 7 to 10 years. Once overt proteinuria develops, renal function progressively declines and end stage renal disease is reached after about 10 years. Hence, the elucidation of molecular pathogenesis of diabetic nephropathy is necessary for the development of effective treatment modalities to prevent onset of diabetic nephropathy to end stage renal disease (ESRD).

PATHOPHYSIOLOGY

Multiple mechanisms contribute to the development and outcomes of diabetic nephropathy (microalbuminuria) and these mechanisms are found to be similar in both adults and pediatric populations.In this review we have focused on the particular factors involved in the pathogenesis of diabetic nephropathy.

Hemodynamic changes:

Under conditions of sustained hyperglycemia, the glomerular cells are affected by various mechanisms. These changes lead to altered structure and function in the glomerulus[2]. In the kidney, the first observed functional change is an abnormally increased GFR[3]. This change develops before any major histological change in the glomerular structure. Later in the development of diabetic nephropathy, typical histologically visible changes seen are : thickened GBM, diffuse glomerulosclerosis, nodular glomerulosclerosis, exudative lesions in the Bowman's capsule , podocyte loss[4], glomerular hyperperfusion and hyperfiltration[5].

The early signs of glomerular hyperperfusion and hyperfiltration result from decreased resistance in both the afferent and efferent arterioles of the glomerulus. The afferent arteriole seems to have a greater decrease in resistance than the efferent. Many factors have been reported to be involved in this defective autoregulation including prostanoids, nitric oxide, vascular endothelial growth factor VEGF (now known as VEGF-A), TGF-β1 and the renin-angiotensin system, specifically angitensin II[6]. These cyclic changes in glomerular volume lead to recurrent episodes of stretch and relaxation of the glomerular structural components, including mesangial cells and podocytes[7,8,9].

Mesangial cells, when exposed to continuous cycle of stretch/ relaxation, alter their morphology. Specifically, these cells change from their normal stellate to a straplike appearance aligning with their long axis perpendicular to the direction of stress[10]. This leads to enhanced proliferation and increased production of extracellular matrix components. This prosclerotic effect of stretch occurs partly as a result of increase in gene and / or protein expression of extracellular matrix components such as collagen I, III and IV, fibronectin, and laminin [10-12].

These hemodynamic changes facilitates albumin leakage from the glomerular capillaries, overproduction of mesangial cell matrix as well as thickening of the glomerular basement membrane and injury to podocytes. In addition, increased mechanical strain resulting from these hemodynamic

changes can induce localized release of some cytokines and growth factors. Mesangial cells are crucial for maintenance of glomerular capillary structure and for the modulation of glomerular filtration via smooth-muscle activity.

Hyperglycemia:

Hyperglycemia is associated with an increase in mesangial cell proliferation and hypertrophy as well as increased matrix production and basement membrane thickening. In vitro studies have demonstrated that hyperglycemia is associated with increased mesangial cell matrix production[13,14] and mesangial cell apoptosis[15,16]. Mesangial cell expansion seems to be mediated in part by an increase in the mesangial cell glucose concentration, since similar changes are observed in mesangial glucose milieu as overexpression of glucose transporters such as GLUT 1 and GLUT 4, thereby increasing glucose entry into the cells. Hyperglycemia might also upregulate VEGF expression in podocytes which could markedly increases vascular permeability[17,18]. There are four mechanisms that explain how hyperglycemia causes tissue damage and diabetic nephropathy: Nonenzymatic glycosylation that generates advanced glycosylation end products, activation of protein kinase C (PKC), acceleration of the aldose reductase pathway[19,20] [Oxidative stress seems to be a theme common to above three pathways[21]] and activation of GPR 91 receptor in the kidney[22].

Dyslipidemia:

Dyslipidemia has been hypothesized to cause kidney damage and to play an important role in the progression of renal failure[23]. In animal models, hyperlipidemic diets worsen renal injury and lipid-lowering strategies ameliorate renal injury[24,25,26,27]. Dyslipidemia may damage glomerular capillary endothelial and mesangial cells as well as podocytes. Mesangial cells express receptors for LDL and oxidized LDL, which upon activation induce mesangial cell proliferation, increase mesangial matrix deposition and enhance the production of chemokines (such as macrophage chemo-attractant protein-1), cytokines (such as interleukin 6) or growth factors. Macrophage chemo-attractant protein-1 enhances the recruitment of macrophages which can infiltrate the glomerulus and become foam cells that release cytokines. Oxidized LDL increases the adhesion of monocytes to glomerular endothelial cells favoring monocyte infiltration and affects tubular epithelial cells[27]. Hypercholesterolemia and hypertriglyceridemia are also associated with podocyte injury which secondarily leads to mesangial sclerosis[25]. Oxidized LDL induces apoptosis of podocytes and nephrin loss (a key component of the glomerular filtration barrier) and increases albumin diffusion in podocyte monolayers in vitro[28].

A number of studies have shown an increased association between patients with microalbuminuria and abnormalities in serum lipoproteins. These

lipid abnormalities include a low level of high density lipoprotein (HDL) as well as high values of low density lipoprotein (LDL), total cholesterol, triglycerides and increased levels of lipoprotein (a). In a cross-sectional analysis of 1160 Type 1 diabetic individuals in the Diabetes Control and Complications Trial (DCCT), progressive increases in albuminuria were associated with elevations in proatherogenic intermediate density lipoproteins and small dense LDL particles[29]. In addition, among both diabetic and non-diabetic patients with reduced serum HDL cholesterol[30,31,32,33,34], the most consistent association between lipoprotein abnormalities and microalbuminuria was with the low HDL. This suggests that clearance of LDL cholesterol may be as important as lower levels of this lipoprotein subfraction to avoid cellular injury. Thus, the apparent association between microalbuminuria and cardiovascular disease may be related to this adverse risk factor profile.

Prorenin:

Initial clinical studies in children and adolescents suggest that increased plasma prorenin activity is a risk factor for the development of diabetic nephropathy[35,36]. The prorenin receptor in the kidney is recently identified and characterized[37-40]. The prorenin receptor in the kidney is located in the mesangium as well as podocytes and its blockade has a beneficial effect on kidneys in animal models of diabetes.

Angiogenic And Proinflammatory Factors:

Recent studies suggest that an inflammatory mechanism mediated by macrophages and angiogenesis may play important roles in the pathogenesis of diabetic nephropathy. Relatively recent reports [41-43] described that the degree of neovascularization was significantly increased in patients with diabetic nephropathy and correlates with the expression of VEGF and angiopoietin which are likely to contribute to diabetic nephropathy by promoting vessel leakage and reducing transendothelial electrical resistance. The angiogenic growth factor VEGF induces the activation of matrix-degrading protease represented by matrix metalloproteases and migration and proliferation of endothelial cells[44]. Recent animal studies utilizing a neutralizing anti-VEGF antibody further demonstrated the involvement of this factor in early glomerular hypertrophy and mesangial matrix accumulation in the progressive stage of diabetic nephropathy. TGF-β has been recognized as a profibrotic growth factor involved in the expansion of mesangial matrix and renal hypertrophy in diabetic nephropathy.

Immunological studies on mechanisms of Diabetic nephropathy:

Recently increased levels of inflammatory markers such as C-reactive protein and interleukin-6 were found to be present in type 1 diabetic patients with micro or macroalbuminuria [45]. Other inflammatory cytokines also contribute to the development and progression of diabetic nephropathy,

specifically interleukin-1 (IL-1), IL-8 and tumor necrosis factor. Concentrations of all these cytokines were increased in models of diabetic nephropathy and seemed to affect the disease via multiple mechanisms [46]. This finding suggests that the pathogenetic mechanisms of diabetic nephropathy also involve the immunological and inflammatory process.

Oxidative Stress:

Generally, metabolic activity within the nephron produces a large amount of reactive oxygen species that are counter balanced by a large number of antioxidant enzymes and free radical scavenging systems. Reactive oxygen species mediate many negative biological effects including peroxidation of cell membrane lipids, oxidation of proteins, renal vasoconstriction and damage to DNA. Hyperglycemia specifically induces oxidative stress even before diabetes becomes clinically apparent. Concentrations of markers of DNA damage induced by reactive oxygen species are higher in patients with more severe nephropathy.

Endothelial Cell Dysfunction (ECD):

Diabetic nephropathy is preceded by glomerular hyperperfusion and hyperfiltration which occur early in type1 and in some 15-44% of type 2 diabetic patients at diagnosis and these play a pathogenetic role in ECD, the early stage of diabetic nephropathy[47-50]. Endothelial cell dysfunction (ECD) is therefore defined as decreased synthesis, release, and/ or activity of endothelial-

derived nitric oxide. The pathophysiology of ECD expressed in various degrees is emerging as a hallmark of several highly prevalent renal as well as cardiovascular diseases and other chronic diabetic complications[51].

Podocyte Damage And Nephrin Loss:

Recent data suggest that the podocytes, the specialized visceral epithelial cells are important for the maintenance of the dynamic functional barrier[52] and the number of podocytes may be reduced in the glomeruli of both type1 and type2 diabetic patients[53,54]. Furthermore, it has been reported that nephrin, a recently found podocyte protein is crucial for maintaining the integrity of the interpodocyte slit membrane structure and for maintenance of an intact filtration barrier. In diabetic nephropathy, the protein level of nephrin decreases possibly via loss into the urine due to synthesis of splice variant isoforms of the nephrin lacking a transmembrane domain [55,56].

Genetic Susceptibility :

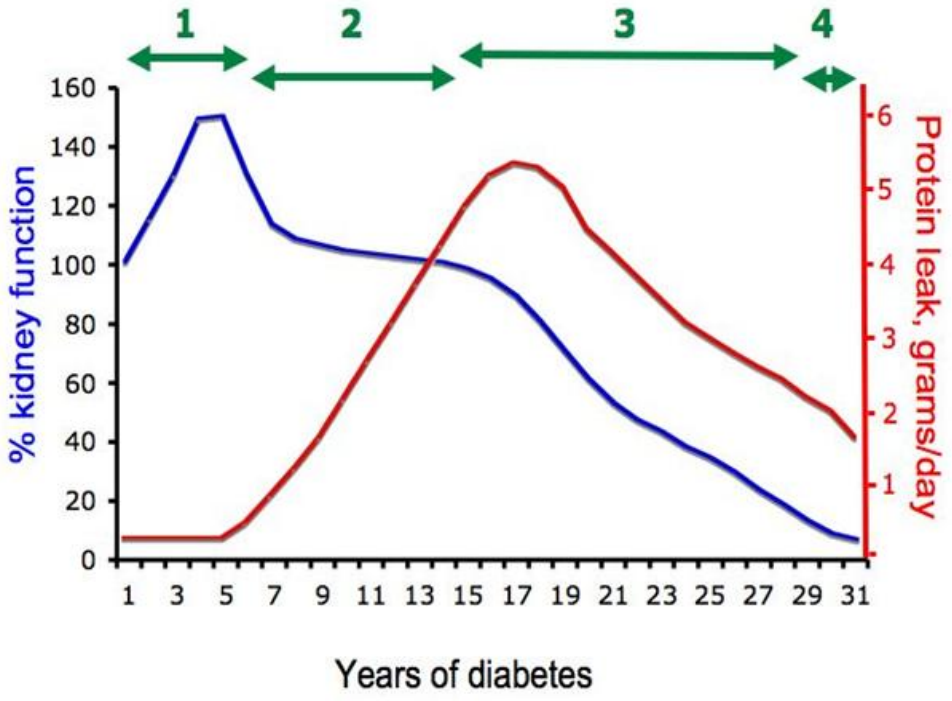
Genotype seems to be an important determinant of both incidence and severity of diabetic nephropathy [57-59]. The increase in risk cannot be explained by the duration of diabetes, hypertension or the degree of glycemic control. Environmental and genetic factors must, therefore have roles in the pathogenesis of diabetic nephropathy. In patients with type1 diabetes, the likelihood of developing diabetic nephropathy is markedly increased in those who have a sibling or parent with diabetic nephropathy[60,61]. There is also

growing evidence that the genetic background determines the risk of nephropathy in patients with diabetes. Epidemiologic studies have shown that 35% of the patients with diabetes develop nephropathy irrespective of glycemic control [62,63].

Symbol	Name	Locus	Rationale
SLC12A3	Solute carrier family 12 member (sodium / chloride) 3	16q13	The SLC12A3 gene encodes a thiazide - sensitive Na^+ - Cl^- cotransporter that mediates reabsorption of Na^+ and of Cl^- at the renal distal convoluted tubule
ELMO1	Engulfment and cell motility 1	7p14.1	ELMO1 contributes to glomerular injury through dysregulation of the ECM metabolism and reduction in cell-adhesive properties to ECMs
ICAM-1*	Intracellular adhesion molecule	19p13	Increased ICAM- 1 expression accompanies progression of type 1 diabetes and diabetic nephropathy
VEGF*	Vascular endothelial growth factor	6p12	VEGF expression increased in glomeruli of diabetic animals; anti-VEGF therapy reduced AER and hyperfiltration.
MBL2*	Mannose- binding lectin	10q11.2-q21	The MBL pathway of complement activation may contribute to the development of diabetic microvascular complications
SUMO4*	Small ubiquitin – like modifier 4	6q25	SUMO mRNA is mainly expressed in kidneys and immune system.
TNF α*	Tumor necrosis factor α	6p21.3	The level of expression of TNF α correlated with obesity and hyperinsulinemia.
TGF-β*	Transforming growth factor – β 1	19q13.1	TGF-β mRNA and proteins (and TGF-β receptor mRNA) identified in rodent glomerular cells.
MCP-1*	Monocyte chemotactic protein - 1	17q11.2-q12	MCP- 1 is produced in response to proinflammatory stimuli and high glucose level in mesangial cells.
*Common genetic determinants for the development of type 1 diabetes and diabetic nephropathy.			

ECM – Extra Cellular Matrix, AER - Albumin Excretion Rate

STAGES OF DIABETIC NEPHROPATHY



Stage 1 (Very early diabetes)

- Increased demand upon the kidneys is indicated by an above normal GFR.

Stage 2 (Developing diabetes)

- The GFR remains elevated or has returned to normal, but glomerular damage has progressed to significant microalbuminuria.
- 30 mg of albumin in the urine over a 24-hour period .

- Without specific interventions 80% of subjects who develop sustained microalbuminuria have their urinary albumin excretion increased at a rate of 10–20% per year to the stage of overt nephropathy or clinical albuminuria over a period of 10–15 years

Stage 3 (Overt or dipstick-positive diabetes)

- Glomerular damage has progressed to clinical albuminuria.
- The urine is "dipstick positive".
- more than 300 mg of albumin in a 24-hour period.
- Hypertension typically develops during this stage
- Once overt nephropathy occurs, without specific interventions the glomerular filtration rate (GFR) gradually falls over a period of several years at a rate that is highly variable from individual to individual (2 to 20 ml / min/ each year).
- ESRD develops in 50% of individuals with overt nephropathy within 10 years and in >75% by 20 years

Stage 4 (Late stage diabetes).

- The kidney's filtering ability has begun to decline steadily.
- Blood urea nitrogen (BUN) and creatinine (Cr) has begun to increase.

- The glomerular filtration rate (GFR) decreases about 10% annually.
- Almost all patients have hypertension at stage 4.

Stage 5 (End stage renal disease, ESRD)

- GFR has fallen to approximately 10 milliliters per minute (<10 ml/min).
- Renal replacement therapy (i.e., hemodialysis, peritoneal dialysis, kidney transplantation) is needed.

SCREENING AND DIAGNOSIS

The American Diabetes Association (ADA) recommends yearly screening for those with type 1 diabetes after 5 yr duration of disease (but not before puberty)[64]. However, the prevalence of microalbuminuria before 5 years in this group can reach 18%, especially in patients with poor glycemic and lipid control and high normal blood pressure levels [65]. Furthermore, puberty is an independent risk factor for microalbuminuria[66]. Therefore, in type 1 diabetes, screening for microalbuminuria might be performed 1 year after diabetes diagnosis, especially in patients with poor metabolic control and after the onset of puberty. If microalbuminuria is absent, the screening must be repeated annually for both type 1 and 2 diabetic patients [64]. However , the Nelson Textbook of Pediatrics recommends screening for microalbuminuria after 5 yrs duration in prepubertal children and after 2 yrs in pubertal children.

The first step in the screening and diagnosis of diabetic nephropathy is to measure albumin in a spot urine sample collected either as the first urine in the morning or at random, for example, at the medical visit. This method is accurate, easy to perform and recommended by American Diabetes Association guidelines[64]. Twenty four-hour and timed urine collections are cumbersome and prone to errors related to collecting samples or recording of time. The results of albumin measurements in spot collections may be expressed as urinary albumin concentration (mg/l)[67,68] or as urinary albumin-to-creatinine ratio (mg/g or mg/mmol)[64,68,69,70]. Although expressing the results as albumin concentration might be influenced by dilution/concentration of the urine sample, this option is still accurate and cheaper than expression as albumin-to-creatinine ratio[67]. The cutoff value of 17 mg/l in a random urine specimen had a sensitivity of 100% and a specificity of 80% for the diagnosis of microalbuminuria when 24-hr timed urine collection was the reference standard[71]. This value is similar to the cutoff value of 20 mg/l recommended by the European Diabetes Policy Group.

Screening should not be performed in the presence of conditions that increase urine albumin excretion such as urinary tract infection, hematuria, acute febrile illness, vigorous exercise, short-term pronounced hyperglycemia, uncontrolled hypertension, and heart failure [72]. Samples must be refrigerated if they are to be used the same day or the next day and one freeze is acceptable

before measurements [69,70]. Immunoassays routinely used for albumin measurements present adequate diagnostic sensitivity for detection of diabetic nephropathy.

Although the measurement of urine albumin excretion is the cornerstone for the diagnosis of diabetic nephropathy, there are some patients with type 1 diabetes who have decreased glomerular filtration rate (GFR) in the presence of normal urine albumin excretion [73,74] and this phenomenon seems to be more common among female patients with longstanding diabetes, hypertension and/or retinopathy [73]. Although renal biopsy was not performed, this observation was probably related to renal parenchymal disease other than classical diabetic glomerulosclerosis. These studies indicate that normoalbuminuria does not protect from a decrease in GFR in type 1 and type 2 diabetic patients. Therefore, GFR should be routinely estimated and urine albumin excretion routinely measured for a proper screening of diabetic nephropathy.

RISK FACTORS

Diabetic nephropathy develops in, at most 40% of patients with diabetes, even when high glucose levels are maintained for long periods of time. This observation raised the concept that a subset of patients have an increased susceptibility to diabetic nephropathy. Furthermore, epidemiological[75] and familial studies[76–80] have demonstrated that genetic susceptibility contributes to

the development of diabetic nephropathy in patients with both type 1 and type 2 diabetes. The main potentially modifiable diabetic nephropathy initiation and progression factors in susceptible individuals are dietary factors and sustained hyperglycemia[81,82], hypertension[83-85], glomerular hyperfiltration [86-88], smoking [89,90], dyslipidemia [83,91,92] and proteinuria levels [93,94].

PREVENTION AND TREATMENT

PREVENTION: Normoalbuminuric patients

The basis for the prevention of diabetic nephropathy is the treatment of its known risk factors: hyperglycemia,hypertension, smoking, and dyslipidemia. These are also risk factors for cardiovascular disease and should be vigorously treated.

Intensive blood glucose control:

Clinical trials have consistently demonstrated that A1c levels <7% are associated with decreased risk for clinical and structural manifestations of diabetic nephropathy in type 1 diabetic patients. In the Diabetes Control and Complications Trial (DCCT), intensive treatment of diabetes reduced the incidence of microalbuminuria by 39% [94-a]. It is interesting to note that patients randomized to strict glycemic control had a long-lasting reduction of ~40% in the risk for development of microalbuminuria and hypertension 7–8 years after

the end of the DCCT[94-b]. In the UK Prospective Diabetes Study (UKPDS), a 30% risk reduction for the development of microalbuminuria was observed in the group intensively treated for hyperglycemia[94-c]. Moreover, in the Kumamoto Study, intensive glycemic control also reduced the rate of development of micro and macroalbuminuria[94-d]. Therefore, intensive treatment of glycemia aiming at A1c <7% should be pursued as early as possible to prevent the development of microalbuminuria.

Intensive blood pressure control:

Treatment of hypertension dramatically reduces the risk of cardiovascular and microvascular events in patients with diabetes. Hypertension is common in diabetic patients, even when renal involvement is not present. About 40% of type 1 patients with normoalbuminuria have blood pressure levels >140/90 mmHg[94-d-1]. In the UKPDS, a reduction from 154 to 144 mmHg on systolic blood pressure reduced the risk for the development of microalbuminuria by 29% [94-d-2].

Renin-angiotensin system blockade:

The role of ACE inhibitors in the prevention of diabetic nephropathy in patients with type 1 diabetes has not been defined.

PREVENTION : Microalbuminuric patients

Intensive blood glucose control:

The effect of strict glycemic control on the progression from micro- to macroalbuminuria and on the rate of renal function decline in macroalbuminuric patients is still controversial. In the DCCT study, intensified glycemic control did not decrease the rate of progression to macroalbuminuria in patients with type 1 diabetes who were microalbuminuric at the beginning of the study[94-a,94-e]. The Microalbuminuria Collaborative Study Group reported similar findings[94-f]. However, these studies [94-e,f] were underpowered to detect an effect of intensified glycemic control on the progression from micro to macroalbuminuria. Moreover, improvement of glycemic control, especially if associated with lower blood pressure levels reduced the renal function decline in proteinuric type 1 diabetic patients [94-g].

Intensive blood pressure treatment and renin-angiotensin system blockade:

In microalbuminuric type 1 and type 2 diabetic patients, numerous studies have demonstrated that treatment of hypertension irrespective of the agent used, produced a beneficial effect on albuminuria [94-h]. Renin-angiotensin system (RAS) blockade with Angiotensin converting enzyme (ACE) inhibitors or Angiotensin receptor blockers (ARBs) confers an additional benefit on renal function. This renoprotective effect is independent of blood pressure

reduction[94-h,94-i] and may be related to decreased intraglomerular pressure and passage of proteins into the proximal tubule[94-j]. These drugs decrease urine albumin excretion and the rate of progression from microalbuminuria to more advanced stages of diabetic nephropathy. A meta-analysis of 12 trials evaluating 698 nonhypertensive microalbuminuric type 1 diabetic patients showed that treatment with ACE inhibitors decreased the risk of progression to macroalbuminuria by 60% and increased the chances of regression to normoalbuminuria[94-k].

Dyslipidemia:

According to American diabetes association in its panel conducted in 2002, drug therapy has been recommended in children >10 years of age if, after an adequate trial of dietary therapy, LDL levels remain ≥190 mg/dl in those with no CVD risk factors or >160 mg/dl in those with CVD risk factors[94-l,94-m]. The goal LDL cholesterol is <130 mg/dl for children in general and <100 mg/dl in those with diabetes . Based on the above considerations, the panel recommends the following for children and adolescents with lipid values greater than the optimal levels as noted above. Blood glucose control should be maximized and dietary counseling should be provided. Dietary change has been documented to reduce LDL levels[94-n]. The use of products such as Benachol margarine and increasing amounts of soluble fiber should be considered as part of the dietary approach. Follow-up fasting lipid profiles should be performed at

3 months and then at 6 months to determine the effects of blood glucose management and dietary change. If treatment goals are achieved, the lipid profile should be repeated yearly. If after 6 months of optimized blood glucose control and dietary intervention there is no significant improvement in lipid parameters, further intervention is warranted based on LDL levels shown below:

- LDL 100–129 mg/dl: maximize nonpharmacologic treatment.
- LDL 130–159 mg/dl: "consider" medication, basing the treatment decision on the child's complete CVD risk profile, including assessment of blood pressure and family history.
- LDL ≥160 mg/dl: begin medication.

Resins (bile acid sequestrants) continue to be generally recommended as first-choice treatments in this age group. However, compliance rates with this class of medications are so low that therapeutic efficacy is lacking. Therefore, statin drugs are considered[(94-o,94 p)].When statins are used, treatment should begin at the lowest available dose and dose increases should be based on LDL levels and side effects.

Elevated triglyceride levels are not directly managed with medication. If the tryglyceride level is ≥150 mg/dl, efforts are made to maximize blood glucose control and achieve desirable weight. If triglycerides are ≥1,000 mg/dl,

significantly increased risk of pancreatitis is present and treatment with a fibric acid medication should be considered.

Multifactorial intervention:

Patients with microalbuminuria frequently have other cardiovascular risk factors such as hypertension and dyslipidemia. The multifactorial intervention consisted of a stepwise implementation of lifestyle changes and pharmacological therapy including a low-fat diet, a three to five times a week of good exercise program, a smoking cessation program and prescription of ACE inhibitors or ARBs and aspirin.

In the last few years, we have witnessed enormous progress in the understanding of the risk factors and mechanisms of diabetic nephropathy, the stages of renal involvement in diabetes and the treatment strategies to prevent or interrupt the progression of diabetic nephropathy. Early detection of diabetic nephropathy, adoption of multifactorial interventions targeting the main risk factors (hyperglycemia, hypertension, dyslipidemia) and use of agents with a renoprotective effect (ACE inhibitors and/or ARBs) do indeed reduce the progression of renal disease. Attention to these procedures will also ensure the reduction of cardiovascular mortality.

AIMS AND OBJECTIVES OF THE STUDY

1. To estimate the prevalence of microalbuminuria in type 1 diabetic patients ≤ 18 yrs of age attending diabetology clinic, Govt Rajaji Hospital, Madurai.
2. To study the associated risk factors in the development of microalbuminuria.

MATERIALS & METHODS

This study was conducted at Government Rajaji Hospital,Madurai Medical College,Madurai.

Study Type:

Observational study

Duration of the study:

August 2010 to November 2011

Study Population:

Type 1 Diabetes mellitus patients of age ≤ 18 yrs of age attending Diabetology Clinic at Govt Rajaji Hospital, Madurai.

Selection of cases:

All cases who are regularly attending diabetology OP and those who are willing to participate in this study.

Inclusion criteria:

Onset of type 1 diabetes ≤ 18 yrs

Exclusion criteria:

1. those with fever

2. urine microscopy with pus cells >10/HPF in uncentrifuged sample

3. h/o hematuria

4. cases with overt proteinuria

5. uncontrollable hypertension.

Sample size:

57 cases

Study design:

57 Type 1 diabetic patients of age ≤ 18 yrs attending Diabetology Clinic at GRH, Madurai were included in the study after obtaining informed consent. Details of name, age, sex, address, age of onset of diabetes, duration of diabetes, family h/o and nature of treatment taken were recorded. Detailed clinical examination was done including measurement of blood pressure and BMI.

Fasting blood samples were collected for estimation of lipid profile, HbA1C, renal parameters and S.calcium. Urine samples collected in sterile containers for estimation of microalbuminuria and repeated at 3 months intervals, only in positive cases to look for persistence of microalbuminuria. HbA1C and microalbuminuria were estimated by immunoturbidimetric method and lipid profile by enzymatic method.

X-ray, ECG and ECHO were taken for all cases. USG abdomen was taken for microalbuminuria positive cases only. Ophthalmological evaluation for diabetic retinopathy was done in all cases.

Ethical clearance:

Ethical clearance obtained from the Ethical committee, Govt. Rajaji Hospital and Madurai Medical College, Madurai.

Definition of variables:

Normal values for biochemical investigations done in this study are,

Microalbuminuria	-	< 20 mg/l
HbA1C	-	≤ 7%
Total cholesterol	-	<190 mg%
HDLcholesterol	-	>20 mg%
LDLcholesterol	-	<130 mg%
Triglycerides	-	<150mg%

Reference values for lipid profile in Indian children were taken from cut off values suggested in Indian Pediatrics Nov 1995.

Statistical analysis done by SPSS 17 Statistics software.

RESULTS AND ANALYSIS

Total no of cases : 57

No. of persistent microalbuminuric cases : 7

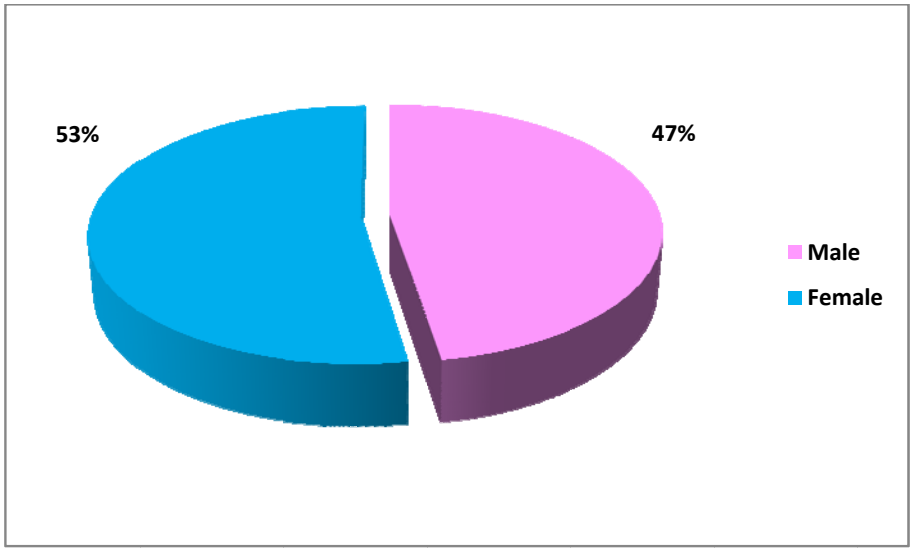
The prevalence of microalbuminuria among Type 1 diabetic patients in this study was 12.28%

SEX:

1. This study included 27 males and 30 females .

SEX	NUMBER	PERCENTAGE
Males	27	47.37%
Females	30	52.63%

Sex incidence of Type 1 DM



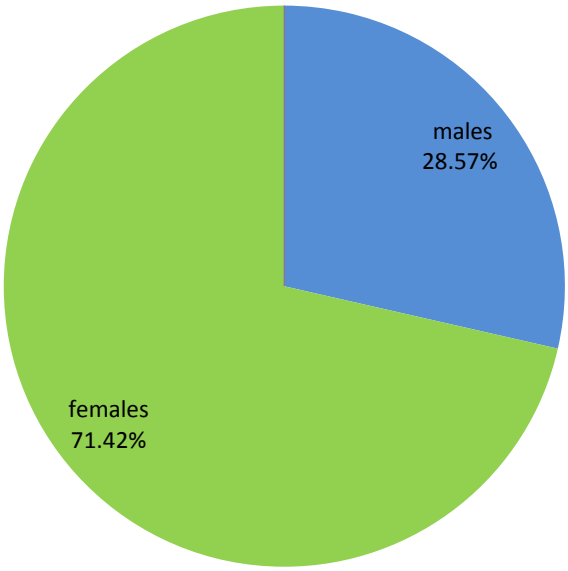
The above results show a slight female preponderance over males in the incidence of Type 1 Diabetes Mellitus.

2. Among the 7 microalbuminuric cases,

No.of.microalbuminuric males - 2 cases (28.57%)

No.of.microalbuminuric females - 5 cases (71.42%)

Sex incidence of microalbuminuria



The male to female ratio was 1 : 2.5.

No statistical significance was found with this gender preponderance.

FAMILY H/O DIABETES:

23/57 (40.35%) cases had family h/o diabetes mellitus (Type 2).

3/57 (5.26%) cases had one of their parents as diabetic (Type 2).

20/57 (35.08%) cases had one of family members (other than 1st degree relatives) to be a diabetic.

DKA EPISODES:

22/57 (38.5%) cases had h/o ICU admission for DKA

HYPOGLYCEMIC EPISODES:

Almost all cases had h/o suggestive of hypoglycemic episodes (blood sugar values not documented)

AGEWISE DISTRIBUTION OF TYPE 1 DIABETES IN THE STUDY:

AGE GROUP	NO. OF DIABETICS
1 - 5	NIL
6-10	7
11 – 15	27
16 – 18	23

AGE GROUP	NO OF DIABETICS
< 12 yrs	12
>12 yrs	45

Minimum age - 7 yrs

Maximum age - 18 yrs

Mean age - 14.32 ± 2.929 yrs

MEAN AGE	NORMOALBUMINURICS	MICROALBUMINURICS
Minimum age	7 yrs	14 yrs
Maximum age	18 yrs	18 yrs
Mean age	14.10 ± 3.032 yrs	15.86 ± 1.345 yrs

No significant relation was found between mean age in normoalbuminurics and microalbuminurics.

AGE OF ONSET OF TYPE 1 DIABETES:

Age of onset ≤ 12 yrs - 43 cases

Age of onset > 12 yrs - 14 cases

Minimum age of onset - 1yr 6months

Maximum age of onset - 16 yrs

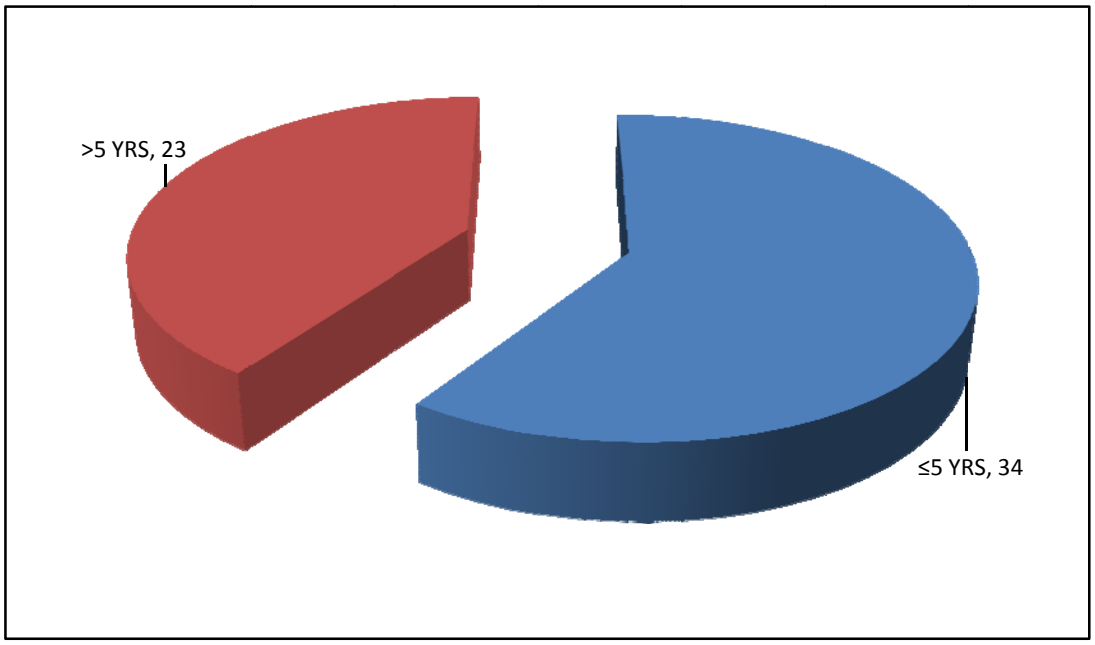
Mean age of onset - 8.965 ± 4.135 yrs

AGE OF ONSET	NORMOALBUMINURICS	MICROALBUMINURICS
Minimum age of onset	1.5 yrs	6 yrs
Maximum age of onset	16 yrs	12 yrs
Mean age of onset	8.980 ± 4.340 yrs	8.857 ± 2.410 yrs

No significant difference found between the mean age of onset between normoalbuminurics and microalbuminurics.

DURATION OF DIABETES :

Minimum duration	-	6 months
Maximum duration	-	15yrs 6months
Mean duration of diabetes	-	5.36 ± 3.765yrs
≤ 5 yrs duration	-	34 cases
>5 yrs duration	-	23 cases



DURATION OF DIABETES	NORMOALBUMINURICS	MICROALBUMINURICS
Minimum duration	6 months	3 yrs
Maximum duration	15.5 yrs	10 yrs
Mean duration	5.130 ± 3.802 yrs	7.000 ± 3.266 yrs

Though the mean duration of diabetes in microalbuminurics is higher than that in normoalbuminurics, it is not statistically significant.

Among microalbuminurics ,

patients ≤ 5 yrs duration = 3cases (42.85%)

patients > 5yrs duration = 4cases (57.15%)

- all cases had HbA1c > 7%
- the earliest period of detection of microalbuminuria was at 3 yrs of duration of diabetes
- Statistical analysis done by tests of significance of proportions between the two groups of duration of diabetes ≤ 5 yrs and > 5 yrs (Zc = 0.923), revealed no significant difference in screening for microalbuminuria in ≤ 5 yrs or > 5 yrs duration of diabetes.

BODY MASS INDEX:

4/57 cases had BMI > 95th percentile

Among the above 4 cases , 2 cases had microalbuminuria.

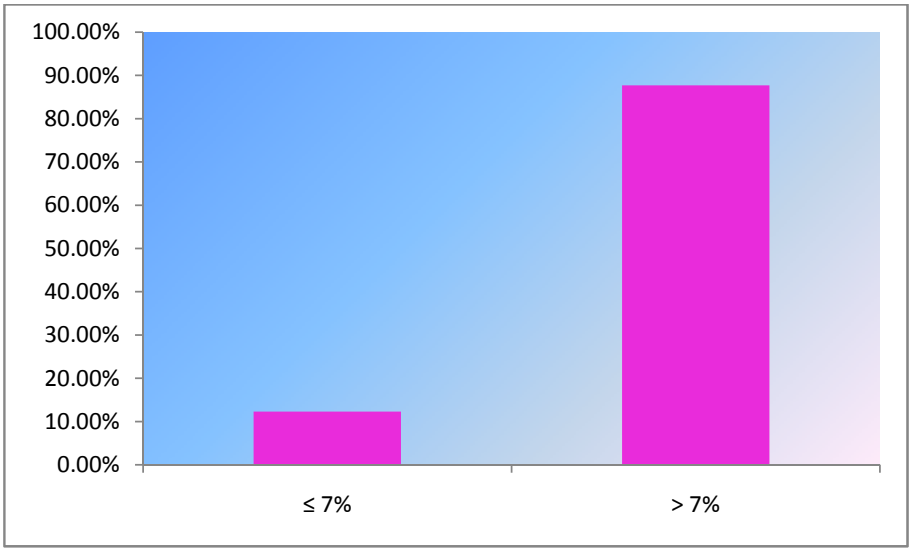
Statistical analysis showed significant correlation between high BMI and presence of microalbuminuria (p value = 0.02).

HbA1C :

Ranged from 5.7 % - 15.8 %

≤ 7% - 7 cases (12.28%)

>7% - 50 cases (87.72%)



HbA1C

HbA1C	NORMOALBUMINURICS	MICROALBUMINURICS
Minimum value	5.4	7.7
Maximum value	15.8	11.4
Mean value	9.704 ± 2.676	9.543 ± 1.384

No significant correlation exist between HbA1C and microalbuminuria.

LIPID PROFILE ANALYSIS :

TOTAL : 57 patients (30 females & 27 males).

Total cholesterol ranged from 95mg% to 277mg%.

HDL ranged from 19 mg% to 47mg%.

LDL ranged from 42mg% to 140mg%.

VLDL ranged from 12mg% to 49mg% and

Triglycerides ranged from 24mg% to 302mg%.

12/57 cases (21 %) had dyslipidemia

All the 12 patients had elevated HbA1C (> 7 %)

No dyslipidemia found in patients with normal HbA1C.

All dyslipidemic children had hypertriglyceridemia (100%) as the primary abnormality. Among these,

6/12 - isolated triglyceridemia

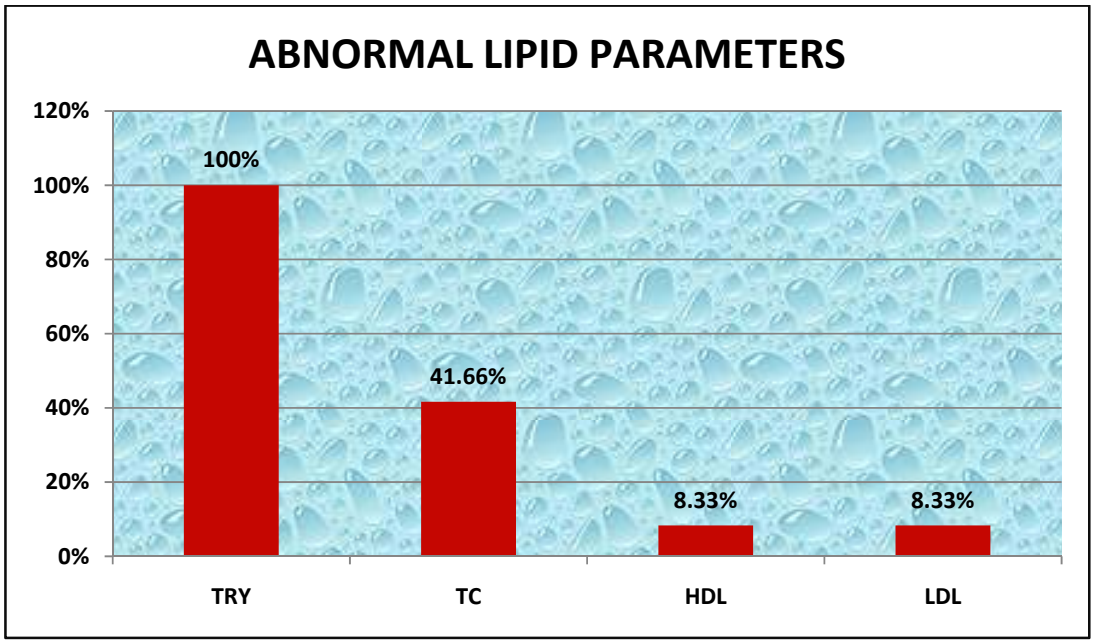
Of the remaining 6 cases with hypertriglyceridemia,

1/6 - had decreased HDL

5/6 - had increased total cholesterol

Of the above 5 cases with hypertriglyceridemia and hypercholesterolemia,

1/6 - had increased LDL also



Females were affected more than the males (5 males & 7 females).

However no statistical significance exist.

3 cases (25%) - with duration of diabetes ≤5 yrs

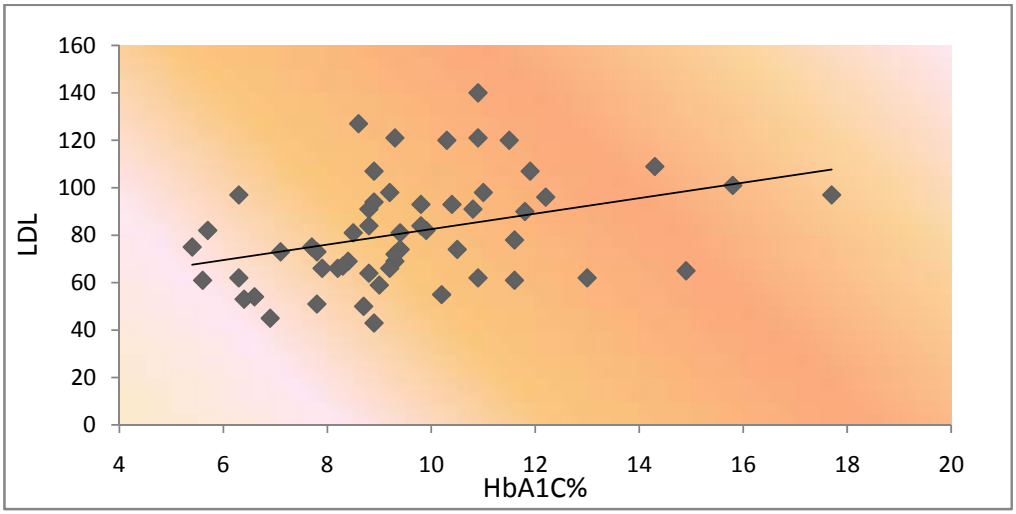
9 cases (75%) - with duration of diabetes >5 yrs

The minimum duration of diabetes at which dyslipidemia was noted was

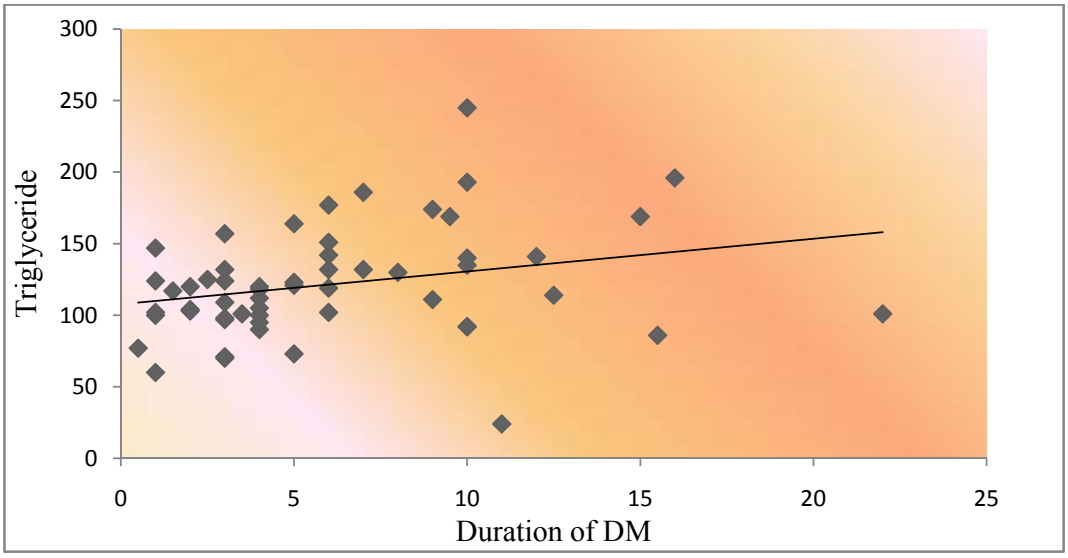
3 yrs.

Statistical analysis done between glycemic control ,duration of diabetes and lipid profile showed,

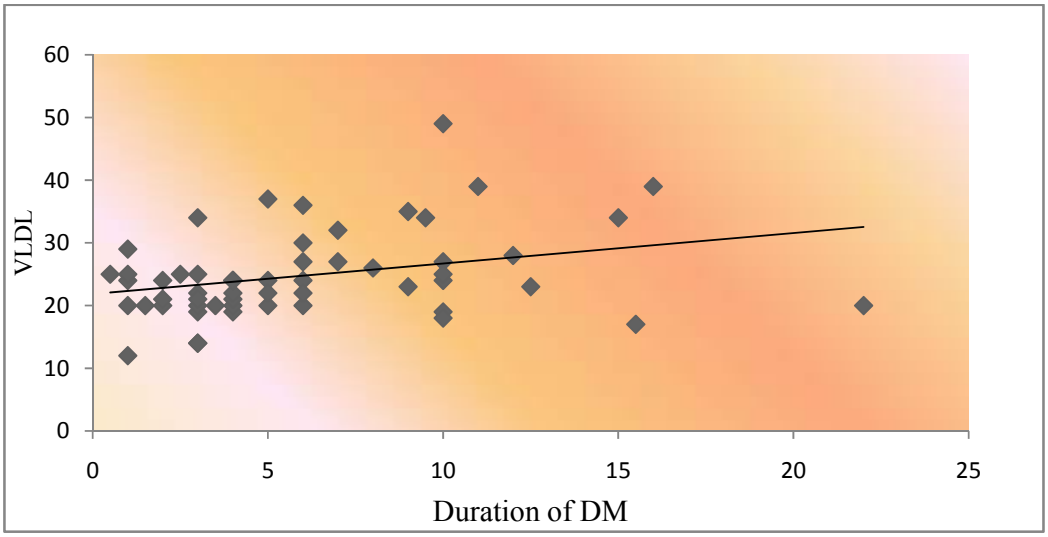
1.Positive correlation between HbA1C and LDL Cholesterol with p value 0.007



2. Statistically significant correlation between Hypertriglyceridemia and duration of diabetes with p value 0.044



3. Significant correlation between VLDL and duration of diabetes with p value 0.043



Microalbuminuria		No.of.cases	Minimum	Maximum	Mean	Std. Deviation
Normo albuminurics	TC	50	97	277	144.34	34.667
	HDL	50	20	47	36.24	6.687
	LDL	50	42	140	81.14	23.085
	TRY	50	24	245	119.62	38.306
microalbuminurics	TC	7	95	231	147.43	49.047
	HDL	7	19	40	27.71	7.697
	LDL	7	51	120	81.71	22.882
	TRY	7	92	302	160.00	69.785

1.The mean Total cholesterol in microalbuminurics (147.43mg%) is significantly higher (p value 0.049) than the mean total cholesterol in normoalbuminurics (144.34mg%).

2.The mean HDL cholesterol in microalbuminurics (27.71mg%) is significantly lower (p value 0.006) than the mean HDL cholesterol in normoalbuminurics (36.24mg%).

3.Though there was a positive correlation between triglycerides and microalbuminuria , it was not statistically significant (p value 0.136).

4.No significant correlation was found between LDL cholesterol and microalbuminuria .

- 3 out of the 12 dyslipidemic cases had microalbuminuria.
- 2 of the above 3 cases were found to have microalbuminuria at the shortest duration of diabetes (3 yrs).

On analysis of the above results , the risk factors for microalbuminuria which had statistical correlation in this study were,

1. Microalbuminuria and BMI (p value 0.020).
2. Microalbuminuria and total cholesterol (p value 0.049).
3. Microalbuminuria and High Density Lipoproteins (p value 0.006).

USG ABDOMEN :

Bilateral medical renal disease is found in 2/7 cases of microalbuminuria

MALES - 1 case with duration of diabetes 3 yrs

FEMALES - 1 case with duration of diabetes 8 yrs

RENAL PARAMETERS:

Blood urea & S.creatinine were normal in all cases .

S.calcium is within normal limits in all cases

BLOOD PRESSURE:

BP is < 95^{th} percentile in all cases

ECG :

Found to be within normal limits in all cases

CHEST X RAY:

Normal study in all cases.

ECHO:

MVP, Trivial MR, Mild diastolic dysfunction were noted in 3 cases respectively. All other cases were found to be normal.

No correlation was found between abnormal cardiovascular function and incidence of microalbuminuria.

DISCUSSION

The total no of cases enrolled in our study were 57, out of which 30 were females and 27 were males. The cumulative prevalence of microalbuminuria in our study was 12.28 %. The studies done by Jorner et al in 1992, Patel et al in 1998 and Schaltz et al in 2001 also showed the prevalence of microalbuminuria to be 12.50% similar to our study .The prevalence of microalbuminuria in type I diabetic children in different studies ranged between 7% and 28.2%.

Author (Ref No)	**Year**	**No of Patients**	**Prevalence (%)**
Jorner et al.(95)	1992	351	12.5
Patel et al. (100)	1998	494	12.5
Schaltz et al. (103)	2001	494	12.5
Baak et al. (96)	1993	70	16
Mathiesen et al. (97)	1995	209	15
Bruno et al. (98)	1996	211	7
Jones et al. (99)	1998	233	14.6
Moore et al. (101)	1999	419	4.29
MIDAC group(102)	2000	1007	9.7
Viswanthan et al. (104)	2002	95	28.2
Moayeri et al (105)	2006	118	19.5

The wide range of prevalence in various studies may be due to difference in ethnic groups (genetic factors are believed to be responsible for the

development of diabetic nephropathy), methodology and definition of microalbuminuria, population size, length of follow up and mean age of study population.

SEX :

Male to female ratio in our study is 1 : 2.5 . The higher incidence of microalbuminuria in females is also found in other studies – 1 : 1.9 in MIDAC and Pittsburg research groups[106,107] confirming that the development of microalbuminuria is accelerated in girls.

AGE:

The mean age of the patients with microalbuminuria (15.86 yrs ± 1.345) was higher than the mean age of the children with normoalbuminuria(14.10 ± 3.032). All cases with microalbuminuria were found to be > 12 yrs of age (after puberty) in our study. This is comparable with the previous studies which had indicated that the onset of microalbuminuria before puberty occurs only rarely and consequently screening for microalbuminuria should be recommended for children over 12 yrs of age [106-108].There are only a few reports of diabetic children who develop diabetic nephropathy in prepubertal period [109,110].

On statistical analysis, there was no significant correlation between the prevalence of microalbuminuria and either the current age of the patients or age of onset of the disease, similar to the Oxford Regional Prospective study (ORPS) cohort [112].

FAMILY H/O DIABETES:

Family history of of type 2 diabetes was present in 40.35% of children. 5.26% had one of the parents to be a diabetic and 35.08% had diabetes in the family members other than 1st degree relatives. Similar study done in Chennai[124] showed 35% with family h/o type 2 diabetes, 2.9% with one of the parents to be diabetic and 27.6% with diabetes in family members. The higher percentage of variables noted in this study could be due to smaller sample size when compared to the Chennai study which had enrolled 432 children .

DURATION OF DIABETES:

The mean duration of diabetes in normoalbuminuric cases was 5.130±3.802 yrs and in microalbuminuric cases was 7.000±3.266 yrs. Though the mean duration of disease in microalbuminuric cases was found to be longer than the mean duration in normal subjects, no correlation was found statistically (p value > 0.05). Similar reports were found in Oxford Regional Prospective study cohort[112] which included 527 children with the mean duration of diabetes of 9.8yrs in both microalbuminurics and normoalbuminurics.

The prevalence of microalbuminuria in children with duration of diabetes >5 yrs was 17.39% and in ≤ 5 yrs was 8.82%. Among the microalbuminuric cases, 42.85% had duration of diabetes ≤ 5 yrs and 57.15% had duration > 5 yrs. In this study, the earliest duration at which microalbuminuria was detected was 3 yrs similar to a norway study, which reported a cumulative prevalence of

microalbuminuria (12.1%) among Type 1 patients who had median diabetes duration of 3.0 years[113]. Statistical analysis done by using the tests of significance of proportions between the two groups (Zc = 0.923), revealed that screening of microalbuminuria in cases with duration of diabetes ≤ 5 yrs is equally significant as that of screening at > 5 yrs duration of disease.As the least duration of diabetes at which microalbuminuria was noted was 3 yrs, this result supports the recent consensus for screening of microalbuminuria which recommends screening to be done as early as 2yrs after diagnosis in postpubertal children and yearly thereafter unlike in prepubertal children where screening is done only after 5 yrs of duration of diabetes.

BMI:

4 cases were found to have BMI > 95th percentile indicating obesity, out of which 3 were female and 1 was a male.

2/4 cases had microalbuminuria. Both of them were females of 16yrs & 17yrs of age with poor glycemic control of HbA1C 7.7% and 10.3% respectively. The duration of diabetes was 10 yrs in both the cases.

In our study there was a significant association between BMI and presence of microalbuminuria (p value 0.02).This is supported by a London study published in 2001 done by Chaturvedi et al[111] which included 1134 cases and stated that BMI is an independent baseline risk factor for the incidence of microalbuminuria.

HbA1C:

HbA1C ranged from 5.4% to 15.8% in the study population. The mean value in normoalbuminuric cases was 9.704% and in microalbuminuric cases was 9.543%. There was no significant difference between these two groups statistically. Similar report was found in a study done by Lutale et al[114] as well as in ORPS cohort[112] with no significant difference in glycemic control levels among normoalbuminuric and microalbuminuric diabetic patients. These studies revealed that despite improvements in glycemic control and numbers of subjects achieving HbA1c targets, the prevalence of microalbuminuria was unaffected. Collectively these data add further weight to the growing body of evidence indicating that factors other than glycemic control may be important in the pathogenesis of microalbuminuria during adolescence[115,116]. Non-modifiable predictors of microalbuminuria in childhood include puberty and female sex[117], indicating that pubertal hormonal changes occurring in adolescents with type 1 diabetes may play a role. Consistent with this hypothesis, some experimental and clinical data have implicated changes in the growth hormone axis and also sex steroids in the development of pathogenic features characteristic of microalbuminuria, namely nephromegaly, glomerular hyperfiltration and basement membrane abnormalities [118,119]. In contrast to this, majority of the studies had revealed significant relation between poor glycemic control and microalbuminuria as stated in the review of literature.

LIPID PROFILE:

In Type I Diabetes Mellitus patients, persistent hyperglycemia increases oxidative parameters and hence lipid peroxidation [120,121]. This leads to dyslipidemia and subsequent cardiovascular morbidity and mortality.

The prevalence of dyslipidemia was found to be 21% in the present study which is comparable with other studies done in Cambridge (20.1%)[122],spain (20%)[123] and Chennai (19%)[124]. Hypertriglyceridemia was the primary abnormality noted in our study. Similar results were found with studies from Chennai which is a close geographical area with comparable food habits.

There was a strong positive correlation between poor glycemic control and LDL cholesterol levels (p value 0.007) in our study. This data agrees with those in the literature [125,126].Our study revealed a positive correlation between hypertriglyceridemia and duration of diabetes (p value 0.044). This has been documented by another study done by Polak et al from Paris[127]. Since VLDL is a derived parameter from triglycerides, there was also a significant positive correlation between VLDL and duration of diabetes (p value 0.043) in this study.

The Bogalusa Heart studies and the Pathological determinants of atherosclerosis in youth (PDAY study) have clearly concluded that poor glycemic control and increase in LDL cholesterol had a strong correlation with atherosclerotic plaque in the form of fatty streaks in main carotid artery and

coronary arteries. The atherosclerotic changes due to dyslipidemia had been demonstrated in adolescents as early as 15 years of age in the PDAY study.

The minimum duration of diabetes at which dyslipidemia was noted was 3yrs in our study indicating the need for early screening of dyslipidemia in type 1 diabetics.

3 cases with dyslipidemia had microalbuminuria.

CASE 1 – 15 yrs old female with 3 yrs of duration of diabetes

Had abnormal triglycerides and HDL.

CASE 2 - 14 yrs old male with 3 yrs of duration of diabetes

Had abnormal triglycerides and total cholesterol.

CASE 3 - 16 yrs old female with 10 yrs of duration of diabetes

Had abnormal triglycerides and total cholesterol.

The mean value of total cholesterol among microalbuminuric cases (147.43 ± 49.047) was significantly higher (p value 0.0449) than among normoalbuminuric cases (144.34 ± 34.667). The mean value of HDL cholesterol was significantly lower (p value 0.006) in microalbuminuric cases (27.71 ± 7.697) than normoalbuminuric cases (36.24 ± 6.687).

The relationship between microalbuminuria and dyslipidemia has not been extensively investigated in young people with type 1 diabetes. With respect to the pediatric populations with diabetes, data from the Oxford Regional

Prospective Study showed that the prevalence of microalbuminuria increased across tertiles of total cholesterol[129], supporting our study. Review of literature states that, the most consistent association between lipoprotein abnormalities and microalbuminuria is the lowering of HDL. The present study also reveals the association between microalbuminuria and low HDL as noted in the literature. A recent German study has shown a predictive value of both LDL cholesterol and triglycerides on the development of persistent microalbuminuria[128]. In the present study, no such correlation was found.

The above statistical analysis reveals that poor glycemic control leads to poor metabolic control in the form of dyslipidemia which may hasten the development of diabetic nephropathy.

RENAL PARAMETERS AND BLOOD PRESSURE:

All the cases had normal blood urea, S.creatinine and S.electrolytes. In all microalbuminuric positive cases, the GFR was > 90 ml/mt/1.73 sq.m indicating stage 2 chronic kidney disease.Blood pressure was < 95th percentile in all cases. S.calcium is within normal limits in all cases. This is consistent with the fact that presence of microalbuminuria denotes early stage of chronic kidney disease with no derangement in renal function. Hence blood pressure was found to be normal in all cases as expected in incipient stage of diabetic nephropathy. As hypertention was not noted in any of the cases in this study, correlation could not be studied with respect to microalbuminuria.

ECG:

In all cases ECG was within normal limits.

CXR:

Normal in all cases.

ECHO:

3/57 cases showed MVP, Trivial MR and Mild diastolic dysfunction respectively. None of the findings were related to diabetic cardiomyopathy. In this study, none of the cases had cardiovascular dysfunction and no correlation was found between abnormal echo findings and microalbuminuria, glycemic control, dyslipidemia and duration of diabetes. According to the study done by Bert et al, Belgium[130], predominantly female diabetic children and adolescents have significant changes in left ventricular dimensions and myocardial relaxation properties as compared with control subjects and seem to be at risk for developing diabetic cardiomyopathy and there was no correlation with HbA1c or diabetes duration similar to our study.

In children with type 1 diabetes, endothelial dysfunction is known to coincide with microalbuminuria. There are no long-term studies with follow-up into late adult life to provide direct estimates of cardiovascular mortality. In children with diabetes, progression of urine albumin excretion (even within the normal range) starts early and is associated with worse cardiovascular outcomes than adults.Hence strict glycemic control , life style modification and ACE

inhibitors are necessary in these cases in order to prevent the progression to cardiovascular disease.

DIABETIC RETINOPATHY:

None of the cases had diabetic retinopathy in this study. A study done by Donaqhue et al [131], showed incidence of diabetic retinopathy in children > 6 yrs of diagnosis to be 24 % along with 2% positive microalbuminuria cases. According to ISPAD Clinical Practice Consensus Guidelines 2009 Compendium, Screening for retinopathy and microalbuminuria should start from 11 years with two years diabetes duration and from 9 years with 5 years duration. Screening for retinopathy is recommended whenever persistent microalbuminuria is confirmed. Hence all microalbuminuric cases in this study are under close follow up for early detection of retinal changes.

CONCLUSION

1. The prevalence of microalbuminuria among type 1 diabetic patients was 12.28%.
2. 3/7 cases (42.85%) had microalbuminuria within 5 yrs of onset of diabetes.
3. The least duration of diabetes at which microalbuminuria was noted was 3 yrs. Screening for microalbuminuria in $\leq$ 5 yrs duration was found to be statistically significant as that of screening juvenile diabetics of more than 5 years duration.
4. Age and gender were not the significant risk factors in the development of microalbuminuria statistically.
5. 50% of patients with BMI > 95^{th} percentile had microalbuminuria and high BMI was found to be a significant risk factor in the development of microalbuminuria.
6. Duration of diabetes was significantly associated with dyslipidemia (hypertriglyceridemia).
7. Poor glycemic control also had strong correlation with dyslipidemia (high LDL cholesterol).
8. Dyslipidemia was found to be significantly associated with microalbuminuria.

a. High total cholesterol and low HDL cholesterol were the significant risk factors in the development of microalbuminuria. Whereas,

b. Triglycerides and LDL cholesterol did not correlate significantly with the development of microalbuminuria.

9. Dyslipidemic cases in this study were in need of intervention in the form of dietary and life style modifications as maximum values were below the recommended level for intervention with medications.
10. Unlike other studies there was no direct correlation between glycemic control and microalbuminuria, indicating that there are important factors other than glycemic control in the pathogenesis of microalbuminuria like genetic susceptibility.
11. Base line renal parameters and blood pressure were normal in microalbuminuric cases similar to normoalbuminuric cases indicating early, reversible, incipient stage of diabetic nephropathy.
12. No evidence of cardiovascular dysfunction/diabetic cardiomyopathy or diabetic retinopathy were found in the study group perpetuating the need for long term follow up.

RECOMMENDATIONS

1. 50% of cases with BMI > 95th percentile had microalbuminuria.Hence maintenance of desirable weight is necessary among juvenile diabetics.

2. The juvenile diabetics with dyslipidemia had microalbuminuria within 5 yrs of onset of diabetes.Hence screening for microalbuminuria and for its risk factors in ≤ 5 yrs duration also is mandatory.

3. In patients with poor glycemic control,there is a need for early screening for dyslipidemia as it is one of the major risk factors in the development of diabetic nephropathy.

4. Early intervention in dyslipidemic cases according to American Diabetes Association (ADA) - 2002 panel should be strictly adhered to prevent the progression of chronic kidney disease.The recommendations of ADA are,

A . For LDL cholesterol

100-129 mg/dl - maximize nonpharmacologic treatment.

130-159 mg/dl - consider medications if cardiovascular disease risk profile present.

>160 mg/dl - begin medications with statins.

B . For Triglycerides

≥150 mg/dl - maximize blood glucose control

- achieve desirable weight

≥1000 mg/dl - consider fibric acid medications

5. Long term follow up is recommended to look for cardiovascular dysfunction and diabetic retinopathy in microalbuminuric cases.

6. Since microalbuminuria indicates early and reversible stage of diabetic nephropathy, early medical intervention with ACE inhibitors is recommended in all microalbuminuric cases as it halts the onset and progression to end stage renal disease.

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College London, Guy's Hospital, London, UK .Professor David B Dunger, University Department of Paediatrics, Box 116, Level 8, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK.of African origin in Dar Es Salaam, Tanzania .Janet JK Lutale, Hrafnkell

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PROFORMA

HISTORY

- Name: Age: Sex: Address:
- Food habits:
- Age of detection of DM:
- Duration of symptoms before detection:
- h/o DM in siblings:
- h/o DM in parents /family members:
- h/o any previous viral illness before detection:
- Associated infection on diagnosis:
- DKA episodes:
- Hypoglycemic episodes:
- Mode of treatment:
- Duration of treatment:

CLINICAL EXAMINATION:

Height: weight: Head circumference:

HR: RR: BP:

RS: CVS: P/A: CNS:

INVESTIGATIONS

- HbA1C
- Average blood sugar
- Microalbuminuria
- Lipid profile
- Blood urea
- S.creatinine
- S.electrolytes
- S.calcium
- Ultrasonogram Abdomen
- X-ray chest
- ECG
- Echocardiogram
- Ophthalmological evaluation for diabetic retinopathy (Fundus examination)

KEY TO MASTER CHART

M	MALE
F	FEMALE
HT	HEIGHT
WT	WEIGHT
N	NORMAL
DM	DIABETIC MELLITUS
CAL	CALCIUM
TC	TOTAL CHOLESTEROL
HDL	HIGH DENSITY LIPOPROTEIN CHOLESTEROL
LDL	LOW DENSITY LIPOPROTEIN CHOLESTEROL
VLDL	VERY LOW DENSITY LIPOPROTEIN CHOLESTEROL
TRY	TRIGLYCERIDES